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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,707	10/27/2005	Masataka Kuwana	4439-4036	2198

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EXAMINER	
DUTT, ADITI	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,707	KUWANA ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9-16,19-20,22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,17,18 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/15/05* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 12 January 2007 has been entered in full. Claims 1, 2, 9, 11, 13-20 have been amended. New claims 21-22 have been added.

2. The amendment to the claims filed on 12 January 2007 is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611, Jun. 30, 2003)* with respect to claims 17 and 18. Specifically, claims 17-18 are presented as "Withdrawn – Currently amended" claims; however, the correct status of the claims is "currently amended". Appropriate correction is required.

Election with traverse

3. Applicant's election with traverse of Group I, claims 1-8 and 17-18, in the reply filed on 12 January 2007 is acknowledged.

4. The traversal is on the ground(s) that all the claims in the application: (i) depend from a monocyte-derived multipotent cell; (ii) is linked to methods of preparing/using the same; (iii) are products of the monocyte-derived multipotent cell; and, therefore, combining all the Groups together would not impose an undue search burden on the Examiner. Applicant, therefore, contends that

Groups II-X, directed to methods, are linked to Group I, reciting the monocyte-derived multipotent cell. It is to be noted, that Groups III-VII comprise product claims and not directed to methods as stated by the Applicant. Additionally, Groups II-X recite the special technical features of progenitor cells induced by culturing the monocyte-derived multipotent cells, methods of preparing a monocyte-derived multipotent cell, and a theuapeutic agent comprising the multipotent cells, each of which is not required by the other method/s or product/s (see pages 3 and 4 of the Office Action dated 15 December 2006). As stated in the previous Office Action, the inventions lack the same or corresponding special technical feature as the prior art teaches the monocyte-derived multipotent cells (see page 3). The "special technical features" means those technical features that define a contribution over the prior art. (See M.P.E.P. 1850). Thus, the apparent "special technical features" of these claims cannot form the basis of unity of invention, and the main invention which forms a single inventive concept is Group I, claims 1-8, 17-18 and 21.

5. Furthermore the methods and products of Inventions I-X lack unity of invention, because the methods are practiced with materially different process steps for materially different purposes and each method requires a non-coextensive search because of different starting materials, process steps and goals. Specifically, the methods of Groups II, VIII-X require administration of functionally and structurally different cell types and agents. In addition, the products of Groups III-VII, are different cell types having characteristically

different cellular morphology and properties, that will differentiate to different cells and tissues and, therefore, represent a patentably distinct invention. Pursuant to 37 C.F.R. § 1.475 (a), Unity of invention before the International Searching Authority, an international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. Groups II-X do not possess special technical features as set forth above. Note that PCT Rule 13 does not provide for multiple products or methods within a single application.

6. Applicant has added new claims 21 and 22, of which claim 21 reads upon the product claim, directed to the monocyte-derived multipotent cell of Group I, and, therefore, will be examined in the current application. Claim 22, reciting a method for preparing the monocyte-derived multipotent cell will not be considered in the instant application for reasons mentioned above.

7. Applicant is reminded that, upon allowance, the first enabled method of using the claimed compound will be rejoined to the examined Invention. However, until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims should be

maintained (*In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b), 1184 O.G. 86 March 26, 1996).

8. **The requirement is still deemed proper and is therefore made FINAL.**

9. Claims 9-16, 19-20 and 22, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12 January 2007.

10. Claims 1-8, 17-18 and 21, drawn to a monocyte-derived multipotent cell differentiating to progenitor cells, and therapeutic agents comprising the cells, are being considered for examination in the instant application.

Drawings

11. The instant drawings do not comply with 37 C.F.R. § 1.84(U)(1), which states that partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. Figure 10 of the instant application, for example, is presented on four separate panels. The four panels of drawings, which are labeled "Figure 10" in the instant specification should be renumbered as "Figures 10A –10D". Similarly, Figure 4 has eight separate panels, which should by renumbered as "Figures 4A……4H". Applicant is reminded that once

the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-8, 17-18 and 21, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 1 is vague and indefinite for recitation "derived from a monocyte". Since the claimed cell is identified as "a monocyte derived", it is not clear if repeating this limitation changes the scope of the claimed subject matter. Applicant is advised that deletion of the limitation would obviate this ground of rejection (see claim 2 for example).

15. Regarding claims 5-7, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

16. Regarding claims 3, 5-8, the limitation "can" renders the claim(s) indefinite because it is not clear if the term is a characteristic of the claimed cell or recitation of capability. Clarification is required.

17. Claims 2, 4, 17, 18 and 21 are indefinite for being dependent from indefinite claims.

Claim Rejections-35 USC § 101 – Non-statutory subject matter

18. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

19. Claims 1-8 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed monocyte-derived multipotent cell, and progenitor cells are not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated", as taught by (page 22, para 1, Example 1) the specification. See MPEP 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 1-8, are rejected under 35 U.S.C. 102(b) as clearly anticipated by Zhao et al., (PNAS 100: 2426-2431, 2003).

21. The claims are directed to a monocyte-derived multipotent cell (MOMC), that expresses CD14, CD34 and CD45, type I collagen, wherein the monocyte after culturing can differentiate into nerve, endothelial cells, mesenchymal, mesodermal cells in culture (claims 1-8).

22. Zhao et al. teach the isolation of pluripotent stem cells from human peripheral blood monocytes, that resemble fibroblasts and express the moncytic and hematopoietic cellular differentiation stem cell markers, such as CD14, CD34 and CD45 (pages 2427-2428, Table 1). Zhao et al. further teach that human peripheral blood cells containing monocytes, when cultured under specific conditions, differentiate into macrophages, lymphocytes, epithelial, neuronal, endothelial and hepatocytes etc. (pages 2428-2430). However, as evidenced in

Stem Cells (NIH, June 2001, pages 32-35), monocytes, macrophages, lymphocytes etc., are cells that belong to the mesenchymal or mesodermal family and, therefore, this limitation is inherent in the teachings of Zhao et al. Thus, Zhao et al. clearly anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claim 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al., (PNAS 100: 2426-2431, 2003), in view of Pujol et al. (Differentiation 65: 287-300, 2000).

25. The claims are directed to a monocyte-derived multipotent cell (MOMC), that expresses CD14, CD34 and CD45, type I collagen, wherein the monocyte is obtained by culturing peripheral blood mononuclear cells (PBMCs) on fibronectin (claim 21).

26. The teachings of Zhao et al. are set forth above.

27. Zhao et al. do not teach PBMC culture in vitro on fibronectin to obtain a monocyte-derived multipotent cell.

28. Pujol et al. teach the culturing of CD14 monocytes derived from PBMC on fibronectin-coated tissue culture plates (page 288, "Cell Culture").

29. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the in vitro culture of PBMCs of Zhao et al. to conduct the culture on fibronectin coated plates as taught by Pujol et al. The person of ordinary skill in the art would have been motivated to make that modification and would have expected success because of its well-established use in tissue-culture methods to promote attachment, spreading and proliferation of various cell types.

30. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Claim Rejections - 35 USC § 112-Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

31. Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

32. The specification does not reasonably provide enablement for using the monocyte-derived multipotent cells (MOMC), mesodermal or neuronal cells, as an active ingredient for a therapeutic agent for the treatment of any disorder, wherein the monocyte-derived cells express CD14, CD34 or CD45, type I collagen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

33. The claims are drawn to monocyte-derived multipotent cells, mesodermal or neuronal cells, as an active ingredient for a therapeutic agent, wherein the monocyte-derived cells express CD14, CD34 or CD45, type I collagen.

34. However, the instant specification as filed, fails to provide enough guidance for one skilled in the art on how to practice the instant invention, thereby requiring undue experimentation to discover how to use Applicant's invention, as currently claimed.

35. The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands,* 8 USPQ2d, 1400 (CAFC 1988).

36. The specification of the instant application teaches that peripheral blood monocytes derived from bone marrow hematopoietic stem cells differentiate into various cell types, such as macrophages, dendritic cells, osteoclasts etc. (page 1, para 2). The specification also teaches that the monocyte-derived multipotent cells (MOMC), cultured on fibronectin coated plates for 7-10 days, demonstrated expression of unique fibroblast like cells, with a positive phenotype of CD14, CD45, CD34 and type I collagen, and can differentiate into phagocytes, mesenchymal cells and other cell types (pages 24-27, Examples 4-7; page 34, Results-Example 18; pages 45-47, Examples 23-24). Furthermore, the specification suggests that MOMC, mesodermal progenitors/stem cells, or neural progenitors/stem cells differentiated from MOMC, can be administered to patients

for the treatment of diseases, e.g. degenerative diseases (pages 20-21). However, the specification does not provide any evidence or sound scientific reasoning that the limited information presented in the disclosure can be directly extrapolated to using MOMC as a therapeutic agent for the treatment of any disorder.

37. Relevant literature teaches that monocyte-derived mesenchymal progenitors (MOMP) having similar morphology to circulating fibrocytes, could express the genes and proteins corresponding to other cell types, such as osteoblasts, skeletal myoblasts, chondrocytes and adipocytes, in culture (Kuwana et al., Jour Leukocyte Biol 74: 833-845, 2003). Fibroblast like cells are also obtained from culture of peripheral blood-derived multipotent mesenchymal stromal cells (PBMSCs), which are capable of differentiating to diverse cell types (He et al., Stem Cells 25: 69-77, 2007; page 69). Additionally, a prior art reference teaches the isolation of unrestricted somatic stem cells from umbilical cord blood, which can differentiate to mesenchymal, hematopoietic and neural progenitor cell (Wernet, UD Patent Application No. US 2002/0164794 A1, dated 7 November 2002, page 1). However, the relevant prior and post art literature does not provide any evidence that MOMC can be used as a therapeutic agent for the treatment of any disorder.

38. Relevant art further teaches that because peripheral blood derived cell types, e.g. PBMSC and MOMP (stated above) have low copy numbers in circulation, the current culture conditions are unable to expand the numbers

resulting in low yields, and low survival rates (He et al., page 73, column 2, para 1; page 75; Kirschstein, R. and Skirboll, LR, Stem Cells, NIH, June 2001, Chapter 5, page 53). Kirschstein, R. and Skirboll, LR, further states that while attempts to increase the yield in cell numbers is in progress, the current state of the assays employed for expansion of blood derived stem cells till date vary, and are not reproducible between different research groups. While modest increases in progenitor cells for granulocytes and macrophages in culture has been reported, it is still not known whether these numbers are clinically beneficial for long term use (Kirschstein and Skirboll, page 54). The state of the stem cell art further reports that an inverse relationship between the progenitor cell division rate and longevity of the stem cells in mice, adds a concern that the current culture conditions for inducing selection of cells might shorten the life term of the cells (page 55). Furthermore, in context to the use of the above cell types, (which have a mixture of cells) for cell-based therapy, He et al., cautions that as only a "few markers for multipotent mesenchymal stem cells have been so far ascertained, both immunoselected and unselected PBMSCs showed a wide diversity in their phenotypes, gene expression profiles and biological behaviors" (page 75, Summary). The plasticity properties of stem cells from blood or bone marrow to differentiate into specific cells and tissues, although being initiated in mice, the research is still in its infancy and one would not be able to extrapolate the plasticity potential of the hematopoietic stem cells in mice to that in humans with predictability (Kirschstein and Skirboll, page 55). While the skill level in the

art is high, the level of predictability is low, thus one skilled in the art would not be able to predict from the instant specification that all possible diseases would be treated by administration of monocyte-derived multipotent cells. The sole working examples in the specification, as originally filed, pertain to monocyte derived cell diffentiation in vitro. While it is not necessary that Applicant understands or discloses the mechanism by which the invention functions, in this case, in the absence of which no extrapolations can be made of the results to in vivo treatment. Undue experimentation would be required to determine such.

39. In vitro conditions do not necessarily mimic in vivo conditions, which involve communication and complex interactions within/between a neuron/cell, to elicit a response. In vitro experiments such as that described in the instant application, are vastly different from in vivo assays, both physiologically or biologically, and in predictability of success, and thus would entail undue experimentation by a skilled artisan (See *Maas*, 9 USPQ2d 1746). For example, the skilled artisan would not be able to predict that all types of agents comprising the stem cell types administration would result in the agents crossing the blood brain barrier, relocating to the target region of the brain and subsequently treating all possible injuries or degenerative disorders.

40. The literature, further discloses that neural stem cells administered systemically will differentiate into hematopoietic cell lineages (and hence, most likely not treat the neurodegenerative disorder) (Bjornson et al., Science 283: 534-537, 1999). There is also little guidance in the specification, as to whether

MOMC or neural stem cells or neural progenitor cells are capable of crossing the blood brain barrier, thereby entailing undue experimentation to determine the therapeutic efficacy of the administered cells. The skilled artisan would not be able to predict that administration of the neural stem cells would result in neural stem cells crossing the blood brain barrier, relocating to the target region of the brain and subsequently treating all possible disorders. Undue experimentation would also be required of the skilled artisan to determine the optimal dosage and type of administration of the stem cells.

41. Due to the large quantity of experimentation necessary to use MOMC as a therapeutic agent; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior and post art which has yet to determine effective and lasting therapeutic measures for various diseases and, the unpredictability of treatment of diseases using stem cells; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Conclusion

42. No claims are allowed.

43. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

44. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

45. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
29 January 2007

OLGA N. CHERNYSHEV, PH.D.
PRIMARY EXAMINER